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(54) COMPOSITIONS FOR APPLICATION TO OR CONSUMPTION BY THE HUMAN BODY AND CONTAINING COMPOUNDS HAVING A PHYSIOLOGICAL COOLING EFFECT

(71) We, WILKINSON SWORD LIMITED, a British Company, of Sword House, High Wycombe, Buckinghamshire, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to compounds having a physiological cooling activity on the body, i.e. compounds which are capable of stimulating the cold receptors of the nervous system of the body, and compositions containing them.

Menthol is well known for its physiological cooling effect on the skin and mucous membranes of the mouth and has been extensively used as a flavouring agent (menthol being a major constituent of oil of peppermint) in foodstuffs, beverages, dentifrices, mouthwashes, etc. and as a component in a wide range of toiletries, liniments and lotions for topical application. Menthol is also a well known tobacco additive for producing a 'cool' sensation in the mouth when smoking.

It is well established that the 'cooling' effect of menthol is a physiological effect due to the direct action of menthol on the nerve endings of the human body responsible for the detection of hot or cold and is not due to latent heat of evaporation. It is believed that the menthol acts as a direct stimulus on the cold receptors at the nerve endings which in turn stimulate the central nervous system.

Although menthol is well established as a physiological coolant its use, in some compositions, is circumscribed by its strong minty odour and its relative volatility.

A few other compounds have been reported in the technical literature as having an odour or flavour similar to menthol and from time to time have been proposed as flavourants or odourants in a variety of topical and ingestible compositions. For example, Japanese Patent Publication No. 39—19627 reports that 3-hydroxy-methyl p-menthane (menthyl carbinol) has a flavour closely resembling that of 1-

menthol and suggests its use as a flavourant in confectionery, chewing gum and tobacco. In Swiss Patent No. 484,032 certain saccharide esters of menthol are proposed as additives to tobacco. In French Patent Specification No. 1,572,332 N,N-dimethyl 2-ethylbutanamide is reported as having a minty odour and refreshing effect, and the minty odour of N,N-diethyl 2,2-dimethylpropanamide is also referred to. A similar effect is reported for N,N-diethyl 2-ethylbutanamide in Berichta *39*, 1223, (1906). A minty odour has also been reported for 2,4,6-trimethylheptan-4-ol and 2,4,6-trimethylhept-2-en-4-ol in Parfums-Cosmetiques-Savons, May 1956, pp. 17—20. The cooling effect of menthol and other related terpene alcohols and their derivatives has also been studied and reported in Koryo, 95, (1970) pp. 39—43. 2,3-p-Methane diol has also been reported as having a sharp cooling taste (Beilstein, Handbuch der Organischen Chemie, 4th Ed. (1923) Vol. 6, p. 744). Still other substituted p-menthanes having a physiological cooling effect are disclosed in German Offenlegungsschrift Nos. P 22 02 535, P 22 03 947, P 22 03 273 and P 22 05 255. Yet other compounds having physiological cooling activity are disclosed in German OLS Nos. P 23 16 999, P 23 17 000, P 23 17 538, P 23 17 539, P 24 13 639, P 23 36 495, P 23 34 985, P 23 45 156 and P 24 39 770.

The present invention is based on the discovery of a group of bicyclic acids, amides, esters and substituted methanols having the property of stimulating the cold receptors of the nervous system of the body and useful for that purpose in a wide range of compositions for topical application to or consumption by the human body including tobacco. This group of bicyclic acids, esters, amides and substituted methanols is represented by compounds of the general formula RX where

R is a saturated or monoethylenically unsaturated alkyl-substituted bicyclic hydrocarbon radical containing a total of from 8—12 carbon atoms and selected from [3.1.1]bicycloheptanes, [2.2.1]bicycloheptanes and hept-5-enes and [2.2.2]bicyclooctanes and oct-5-enes containing from 1—3 C_1—C_5 alkyl substituents;

X is a CH_2OH, COOH, $COOR_1$ or $CONR_2R_3$ group attached to said bicyclic radical at a 2-position, and where R_1 is a hydroxyalkyl or hydroxyalkoxyalkyl radical of from 2—4 carbon atoms;

R_2, when taken separately, is H or C_1—C_5 alkyl;

R_3, when taken separately, is H, C_1—C_5 alkyl, C_1—C_5 hydroxyalkyl or C_3—C_6 alkoxycarbonylalkyl with the proviso that when R_1 is H, then R_2 may also be C_3—C_6 cycloalkyl, phenyl or phenyl containing up to 2 hydroxy, methyl or methoxy substituents; and R_2 and R_3, when taken together, represent a C_4—C_5 alkylene group, the carbon atom chain of which may optionally contain an ether oxygen atom, and forming with the nitrogen to which they are attached a piperidino-, pyrollidino or morpholino group.

In accordance with the present invention, therefore, there are provided consumer products for application to or consumption by the human body into which there is incorporated a means for stimulating the cold receptors of the nervous system of the human body wherein said means comprises an effective amount of one or more compounds of the formula RX, where R and X are as above defined. By consumer products we mean a manufactured product applied to or consumed by the human person for toilet, cosmetic, hygienic, nutritive, curative, prophylactic, or other purposes and constituting a vehicle by means of which the said compounds may be brought into contact with the skin, mucous membranes or other surface tissues of the body, whether external tissues or internal, for example, of the nose, throat, mouth and gastrointestinal tract, and includes liquid and solid phase preparations of an essentially formless nature, e.g. solutions, emulsions, pastes, ointments and powders, solid phase preparations of semi-permanent form, e.g. shaped toilet and cosmetic preparations and shaped edible preparations, whose shaped form is only temporary and which lose that form on use, and articles of permanent form but which are of an essentially disposable nature, e.g. cleansing tissues and toothpicks.

For the avoidance of doubt, the term 'consumer product' as used herein does not extend to liquids and mixtures of liquids, e.g. water and common organic solvents, which act merely as a carrier for the cold receptor stimulant.

The bicyclic compounds useful in this invention are, in most cases, particularly the [2.2.1]bicycloheptanes and heptenes, synthesisable from readily available low cost, naturally occuring starting materials by conventional techniques as hereinafter described. The bicyclic compounds are characterised by the ease with which they crystallise, even when present as isomer mixtures. This

leads to easy recovery and purification procedures which in turn provide low cost compounds of high purity.

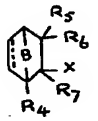
As already indicated, the compounds useful as physiological cooling agents in accordance with this invention are acid, amide, ester and hydroxymethyl derivatives of certain bicyclic hydrocarbons, namely alkyl-substituted [3.1.1]bicycloheptanes, [2.2.1]bicycloheptanes and hept-5-enes and [2.2.2]bicyclooctanes and oct-5-enes containing from 1—3 C_1—C_5 alkyl substituents and a total of from 8—12 carbon atoms. In the case of bicycloheptanes and heptenes, therefore, the substituent alkyl group(s) provides a total of no more than 5 carbon atoms, and in the case of the bicyclooctanes and bicyclooctenes no more than 4. Preferably at least one of the substituent alkyl groups is in an alpha or beta position relative to the acid, ester, amide or hydroxymethyl grouping, which as indicated, is itself attached to the bicyclic group at a 2-position. By reason of cost, availability and activity compounds of the [2.2.1]bicycloheptane and hept-5-ene series are preferred.

Typical bicyclic compounds used in this invention are [3.1.1]bicycloheptane derivatives of the formula

where X is as above defined; illustrative examples of such derivatives being 6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylic acid,

N-ethyl-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxamide and 6,6-dimethylbicyclo[3.1.1]hept-2-yl methanol;

More preferred are [2.2.1]bicycloheptane and heptene derivatives of the formula:



where B is a bridging group selected from —CH_2— and —$C(CH_3)_2$—;

the broken line represents an optional ethylenically unsaturated valency bond;

R_4 is H or CH_3;

R_5 is H or CH_3;

R_6 is H or C_1—C_5 alkyl;

R_7 is H or C_1—C_5 alkyl;

X is as above defined;

it being provided i) that when B is —CH_2— then at least one, but no more than 3 of R_4—R_7, is alkyl, R_4—R_7 together providing a total of from 1—5 carbon atoms;

and ii) that when B is —$C(CH_3)_2$— then R_4 is —CH_3 and R_5—R_7 are all H;

illustrative examples of such compounds being N-ethyl-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxamide, N-[1,7,7]-trimethylbicyclo[2.2.1]heptane-2-carbonyl]glycine ethyl ester, 2-isopropylbicyclo[2.2.1]heptane-2-carboxylic acid, N-methyl-2-isopropylbicyclo[2.2.1]heptane-2-carboxamide, N-ethyl-1,3,3-trimethylbicyclo[2.2.1]heptane-2-carboxamide, N-(3′-hydroxy-n-propyl)-2-isopentylbicyclo[2.2.1]heptane-2-carboxamide, 3,3-dimethylbicyclo[2.2.1]heptane-2-carboxylic acid 2′-hydroxyethyl ester, N-ethyl-2,3-dimethylbicyclo[2.2.1]hept-5-ene-2-carboxamide, N,3-diisopropylbicyclo[2.2.1]hept-5-ene-2-carboxamide, and N,N,3-trimethylbicyclo[2.2.1]hept-5-ene-2-carboxamide; and

[2.2.2]bicyclooctane and octene derivatives of the formula:

where B is —CH_2CH_2—;

the broken line represents an optional ethylenically unsaturated valency bond;

one of R_8 and R_9 is methyl and the other hydrogen;

and X is as above defined;

illustrative bicyclooctane and bicyclooctene derivatives being N-isopropyl-3-methylbicyclo[2.2.2]oct-5-ene-2-carboxamide, N-(1'-ethyl-2'-hydroxyethyl)-2-methylbicyclo[2.2.2]oct-5-ene-2-carboxamide, N-[2-methylbicyclo[2.2.2]oct-5-ene-2-carbonyl]glycine ethyl ester, and N-isopropyl-2-methyl-bicyclo[2.2.2]octane-2-carboxamide.

As will be apparent from the above formulae some of the compounds used as cold receptor stimulants in accordance with this invention exhibit either geometric or optical isomerism or both and, depending on the starting materials and the methods used in their preparation the compounds may be isomerically pure, i.e. consisting of one geometric or optical isomer, or they may be isomeric mixtures, both in the geometric and optical sense. Generally, the compounds will be used as isomeric mixtures, but in some cases the cooling effect may differ as between geometric or optical isomers, and therefore one or other isomer may be preferred.

For the purposes of the present disclosure the following test procedure has been devised as a means to identify compounds having a physiological cooling activity in accordance with the present invention and herein referred to as cold receptor stimulants. This test is intended purely as a means for identifying compounds having a physiological cooling activity and useful in the present invention and for giving an indication of the different relative activities of the compounds, as between themselves and as compared with menthol, when applied in particular manner to a particular part of the body. The results are not necessarily indicative of the activity of these compounds in other formulations and other parts of the body where other factors come into play. For example, a controlling factor in the onset of cooling effect, its intensity and longevity will be the rate of penetration of the compounds through the epidermis and this will vary in different locations on the human body. The formulation of actual products according to this invention will therefore be done largely on an empirical basis although the test results and other figures given herein will be useful as a guide, particularly in the formulation of products for oral administration, since the test procedure to be described involves oral application of the compound. A similar test may, of course, be devised for the purposes of measuring the relative activities of the compounds an another area of the body, for example, the face or forearm, and this will be a useful guide in the choice of compounds to be used in preparations for external topical usage.

It will also be noted that the described test procedure is done on a statistical basis. This is necessary since sensitivity to these compounds will vary not only from compound to compound and from one part of the body to another, but also from one individual to another. Tests of this nature are commonly used in the testing of the organoleptic properties, e.g. taste and smell of organic and inorganic compounds, see Kirk-Othmer: Encyclopedia of Chemical Technology, 2nd Ed. (1967) Vol. 14, pages 336—344.

Test Procedure

The following test procedure is aimed at determining the minimum quantity of the test compound required to product a noticeable cooling effect in a person of average sensitivity, this minimum quantity being termed the threshold for that particular compound. The tests are carried out on a selected panel of 6 people of median sensitivity to l-menthol.

Panel Selection

To select a test panel of average sensitivity the following procedure is used. Known quantities of l-menthol in solution in petroleum ether (bp. 40—60) are placed on 5 mm. squares of filter paper, whereafter the solvent is allowed to evaporate. A panel of observers is enrolled and asked to place one impregnated square at a time on the tongue and to report on the presence or absence of a cooling effect. The quantity of l-menthol on each impregnated square is gradually reduced from a value substantially above 0.25 μg. per square to substantially below 0.25 μg, the precise range being immaterial. Conveniently, one starts with squares containing 2.0 μg l-menthol, the amount on each successive square being half that of the preceding square, i.e. the second test square will contain 1.0 μg, the third 0.5 μg, and so on. Each quantity is tested on the tongue at least 10 times. In this way, the thresholds to cold receptor stimuls by l-menthol are determined for each individual of the panel, the threshold for each individual being that amount of l-menthol for which, in a series of not less than 10 test applications, a cooling effect is reported 50% of the time. Six panel members are now selected whose threshold

to 1-menthol is in the range 0.1 μg to 10 μg and whose average threshold is approximately 0.25 μg, this select panel being regarded as the test panel of average sensitivity.

Compound Testing

To test the activity of compounds according to this invention, the above procedure is repeated using only the 6 selected panel members of average sensitivity to 1-menthol. The individual thresholds for each test compound on each of the 6 selected panel members are determined and averaged. Those compounds whose average threshold on the select test panel is 100 μg or less are regarded as having cooling activity in accordance with this invention.

Test Results

Table I sets out the relative cooling activities of compounds of the formula defined above when tested according to the foregoing procedure. In this Table the bicyclic hydrocarbon radical R, is identified by a reference letter these being further identified in Table II which lists the basic bicyclic hydrocarbon from which the radical R is obtained by the removal of a hydrogen atom at the 2-position.

TABLE I

No.	Compound R	Compound X	b.p. or m.p. °C	Activity g
1	K	—$CONHC_2H_5$	104—5° (mp)	0.5
2	K	—$CONCH(CH_3)_2$	110—11° (mp)	0.7
3	C	—$CONHC_2H_5$	100—2° (mp)	0.7
4	B	—$CONHC_2H_5$	90° (mp)	1
5	B	—$CON(CH_3)_2$	45—47° (mp)	1
6	J	—$CONHC_2H_5$	115—8°/0.01 mm.	1
7	J	—$CONHCH_2COOCH_3$	145°/0.01 mm.	1
8	K	—$CONHCH_2CH(CH_3)_2$	117—9°/0.03 mm.	1
9	K	—$CONHCH_2COOC_2H_5$	99—101 (mp)	1
10	O	—$CONH(o—CH_3,p—CH_3OC_6H_4)$	104—6° (mp)	1
11	P	—$CONH(o—CH_3O,p—CH_3OC_6H_4)$	85—7° (mp)	1
12	P	—$CONHC(CH_3)_2CH_2OH$	102—4° (mp)	1
13	A	—$CONHC_2H_5$	120—4°/0.5 mm	1.5
14	S	—$CONHCH_3$	116—8° (mp)	1.5
15	A	—$CONHC(CH_3)_2CH_2OH$	104—5° (mp)	2
16	A	—$CONHCH(CH_3)_2$	109—11° (mp)	2
17	B	—CH_2OH	55°/0.005 mm	2
8	E	—$CONHC_2H_5$	97—8°/0.1 mm	2
19	K	—$COOCH_2CH_2OH$	94—8°/0.02 mm	2
20	L	—$CONHC_2H_5$	90—1°/0.005 mm	2
21	S	—$CONHC_2H_5$	149—50° (mp)	2

TABLE I Continued)

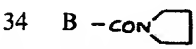
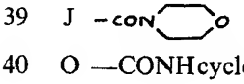
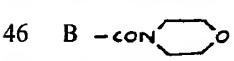
22	E	—CH_2OH	74—8°/0.05 mm	2.5
23	B	—$CONHC(CH_3)_2CH_2OH$	130°/0.005 mm	3
24	E	—$COOCH_2CH_2OH$	78—80/0.005 mm	3
25	F	—$CONHC_2H_5$	88—92°/0.01 mm	3
26	F	—$CONHCH(CH_3)C_2H_5$	96—98° (mp)	3
27	F	—$CONHCH_2CH_2CH_3$	84°/0.01 mm	3
28	J	—$CONHCH_3$	82° (mp)	3
29	J	—$CONHC(CH_3)_2CH_2OH$	69—70° (mp)	3
30	J	—$COOCH_2CH_2OH$	120—2°/0.3 mm	3
31	N	—$CONHC_2H_5$	90—1° (mp)	3
32	O	—$CONHC_2H_5$	110°/0.02 mm	3
33	P		67—8° (mp)	3
34	B		83—5° (mp)	4
35	D	—$CONHCH_3$	110—2° (mp)	4
36	G	—$CONHC_2H_5$	97—103°/0.01 mm	4
37	G	—$CONHCH_2CH_2CH_3$	74°/0.01 mm	4
38	H	—$CONHCH(CH_3)C_2H_5$	123—4° (mp)	4
39	J		127—30°/0.01 mm	4
40	O	—$CONHcycloC_5H_9$	102—4° (mp)	4
41	P	—$CONH(p—CH_3OC_6H_5)$	138—40° (mp)	4
42	S	—$CONHCH(CH_3)_2$	122—4° (mp)	4
43	A	—$CON(CH_3)(CH_2CH_2OH)$	125—30°/0.02 mm	4
44	T	—$CONHCH(CH_3)_2$	135—6° (mp)	4
45	B	—$CONHCH_2COOC_2H_5$	112—3° (mp)	5
46	B		77—9° (mp)	5
47	B	—COOH	112°/0.2 mm	5
48	B	—$COOCH_2CH_2OH$	110°/0.2 mm	5
49	D	—CONH cyclo C_3H_5	135—7° (mp)	5
50	D	—CH_2OH	83°/0.02 mm	5
51	E	—$CONHCH(CH_3)_2$	114—5° (mp)	5
52	M	—$CONHCH(CH_3)_2$	133° (mp)	5
53	O	—$CONH(m—OH, p—CH_3C_6H_4)$	116—8° (mp)	5

TABLE I Continued

54	O	—$CONHCH_2COOC_2H_5$	139°/0.02 mm	5
55	P	—$CONHCH_3$	77—8° (mp)	5
56	A	—$CONHCH_2COOC_2H_5$	104—6° (mp)	6
57	A	—$COOCH_2CH_2OH$	116—8°/0.3 mm	6
58	B	—$CONHCH_3$	139—41° (mp)	6
59	D	—$CONHC_2H_5$	110—2° (mp)	6
60	G	—$CONHCH(CH_3)C_2H_5$	70/0.005 mm	6
61	K	—$CON(t—C_4H_9)(CH_2CH_2OH)$	98—102°/0.01 mm	6
62	N	—$CONHCH(CH_3)_2$	118—9° (mp)	6
63	O	—$COOCH(CH_3)CH(OH)CH_3$	110°/0.05 mm	6
64	D	—$CONHCH_2CHOHCH_3$	59—60° (mp)	7
65	J	—CONH cyclo C_5H_9	80—82° (mp)	7
66	N	—$CONHCH(C_2H_5)CH_2OH$	142—7°/0.02 mm	7
67	A	—$CON(C_2H_5)_2$	95°/0.02 mm	7
68	A	—$CONH(p—CH_3OC_6H_5)$	123—5° (mp)	8
69	A	—$COOCH_2CH_2OCH_2CH_2OH$	145°/0.5 mm	8
70	H	—$CONHC_2H_5$	75—76° (mp)	8
71	I	—$CONHC(CH_3)_2C_2H_5$	128° (mp)	8
72	M	—$CONC(CH_3)_3$	115—8° (mp)	8
73	P	—$CONH(m—OH, p—CH_3C_6H_4)$	72—4° (mp)	8
74	A	—$CON(iso—C_3H_7)(CH_2CH_2OH)$	127°/0.02 mm	8
75	A	—$CON(iso—C_4H_9(C_2H_5)$	100°/0.02 mm	8
76	A		110°/0.02 mm	8
77	E	—$CONHCH(CH_3)CH_2OH$	129—30°/0.005 mm	9
78	F	—$CONHCH_2CH_2CH_2OH$	135°/0.005 mm	9
79	N	—$CONHCH_2COOC_2H_5$	126—32°/0.02 mm	9
80	A	—CONH cyclo C_6H_{11}	141—3° (mp)	9
81	A	—$CONHCH_2CH_2COOC_2H_5$	145°/0.04 mm	9
82	A	—CH_2OH	76—8° (mp)	10
83	S	—$CON(CH_3)_2$	95°/0.2 mm	10
84	S	—$COOCH_2CH_2OH$	122°/0.2 mm	10
85	A	—$CON(CH_2CH_2CH_3)_2$	100°/0.02 mm	10

TABLE I Continued

86	A	—CON(iso C_4H_9)(iso—C_3H_7)	104°/0.02 mm	10
87	Q	—CONHC$(CH_3)_2C_2H_5$	138—40° (mp)	10
88	A	—CONHCH$_2$COOCH$_3$	103—5° (mp)	10
89	I	—CONHC$_2$H$_5$	98—102°/0.01 mm	12
90	I	—CON$(CH_3)_2$	75°/0.25 mm	12
91	A	—CONH$_2$	128—30° (mp)	12
92	I	—COOCH(CH_3)CHOHCH$_3$	100—3°/0.01 mm	14
93	D	—CONHCH$_2$CH$_2$CH$_2$OH	116—8° (mp)	15
94	L	—CH$_3$OH	75°/0.3 mm	15
95	S	—CONHC$(CH_3)_2$CH$_2$OH	153—5° (mp)	15
96	S	—CONH(p—$CH_3OC_6H_5$)	175—7° (mp)	15
97	A	—CON(iso—$C_5H_{11})_2$	125°/0.02 mm	15
98	A	—COOCH(CH_3)CH(OH)CH$_3$	105°/0.01 mm	15
99	A	—CONHCH(CH_3)COOCH$_2$CH$_2$CH$_3$	141°/0.005 mm	15
100	I	—CON(CH_3)(CH$_2$CH$_2$OH)	122—7/0.01 mm	18
101	D	—CONHCH$_2$CH$_2$CH$_3$	125° (mp)	20
102	D	—COOH	125°/0.2 mm	20
103	D	—COOCH$_2$CH(OH)CH$_3$	114°/0.25 mm	20*
104	D	—COOCH(CH_3)CH$_2$OH	,,	
105	E	—CONH(2',5'-dimethylphenyl)	116.5—117.4 (mp)	20
106	E	—CONH(p—$CH_3OC_6H_5$)	111—2° (mp)	20
107	E	—CONHCH$_2$COOCH$_3$	109—10°/0.0025 mm	20
108	E	—COOH	92—3°/0.5 mm	20
109	L	—COOH	79°/0.005 mm	20
110	D	—CONHCH$(CH_3)C_2H_5$	149—151° (mp)	30
111	D	—CONHCH$_2$CH$_2$CH$_2$Ch$_3$	112—4° (mp)	30
112	L	—CONHC$(CH_3)_3$	89—90°/0.005 mm	5

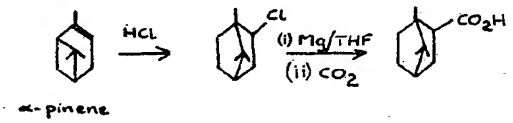
* tested in isomeric mixture.

TABLE II.

Reference letter	Hydrocarbon
A	1,7,7-trimethylbicyclo[2.2.1]heptane
B	2-isopropylbicyclo[2.2.1]heptane
C	1,3,3-trimethylbicyclo[2.2.1]heptane
D	2-isopentylbicyclo[2.2.1]heptane
E	3,3-dimethylbicyclo[2.2.1]heptane
F	2,3-dimethylbicyclo[2.2.1]hept-5-ene
G	3,3-dimethylbicyclo[2.2.1]hept-5-ene
H	2-methylbicyclo[2.2.1]hept-5-ene
I	3-methylbicyclo[2.2.1]hept-5-ene
J	3-*n*-propylbicyclo[2.2.1]hept-5-ene
K	3-isopropylbicyclo[2.2.1]hept-5-ene
L	6,6-dimethylbicyclo[3.1.1]hept-5-ene
M	3-methylbicyclo[2.2.2]oct-5-ene
N	2-methylbicyclo[2.2.2]oct-5-ene
O	3-*n*-butylbicyclo[2.2.1]hept-5-ene
P	3-isobutylbicyclo[2.2.1]hept-5-ene
Q	3-methylbicyclo[2.2.1]heptane
S	3-isopropylbicyclo[2.2.1]heptane
T	2-methylbicyclo[2.2.2]octane.

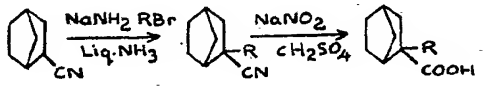
Broadly speaking the bicyclic compounds of this invention can be prepared by standard procedures for the preparation of bicyclic compounds, the following procedures being illustrative:

(i)



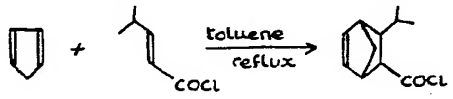
see 'The Terpenes', Vol. II, by J. Simonsen, (2nd Edition), pp. 156, 343.

(ii)



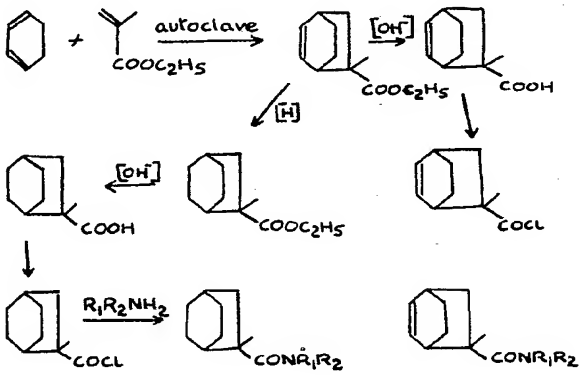
e.g. see W. R. Boehme et al. J.A.C.S. (1958), *80*, 5488—5495.

(iii)

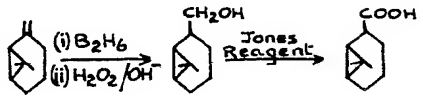


e.g. J. G. Martin et al., Chem. Rev. (1961, 537. 'Diels-Alder Reactions', by A. Wadderman.

(iv)



(v)



e.g. see 'Hydroboration', by H. C. Brown, p. 15
'Reagents for Organic Synthesis', Vol. I, by L. F. and M. Fieser, p. 143.

Turning now to the compositions provided in accordance with this invention, these, as already indicated, may broadly be defined as consumer products for topical application to or consumption by the human body.

Typical consumer products into which the compounds of this invention may be incorporated as cooling agents and which may therefore serve as vehicles for application of the compounds to the person are:

1. Edible and potable compositions including alcoholic and non-alcoholic beverages; confectionery, chewing gum, cachous, ice cream; jellies;

2. Toiletries including after-shave lotions, shaving soaps, creams and foams, toilet water deodorants and antiperspirants, "solid colognes", toilet soaps, bath oils and salts, shampoos, hair oils, talcum powders, face creams, hand creams, sunburn lotions, cleansing tissues, dentifrices, toothpicks, mouthwashes, hair tonics, eyedrops;

3. Medicaments including antiseptic ointments, pile ointments, liniments, lotions, decongestants, counter-irritants, cough mixtures, throat lozenges, antacid and indigestion preparations, and analgesics;

4. Miscellaneous compositions such as water soluble adhesive compositions for envelopes, postage stamps and adhesive labels.

5. Tobacco and tobacco-containing preparations, e.g. cigarettes, pipe tobacco, chewing tobacco, snuff and cigars.

As will be seen the above products can broadly be divided into ingestibles and topicals, both terms being taken in their broadest possible sense. Thus ingestible is to be taken as including not only foodstuffs and beverages taken into the mouth and swallowed, but also other orally ingested products taken for reasons other than their nutritional value, e.g. indigestion tablets, antacid preparations and laxatives. Ingestible is also to be taken to include edible compositions taken by mouth, but not necessarily swallowed, e.g. chewing gum. Topical is to be taken as including not only compositions such as perfumes, powders and other toiletries, lotions, liniments, oils and ointments, applied for the external surfaces of the human body, whether for medical or other reasons, but also compositions applied to or which, in normal usage, come in contact with, internal mucous membranes of the body, such as those of the nose, mouth, or throat, whether by direct or indirect

application, mouthwash and gargle compositions. Topical products, in this context, also include toilet articles such as cleansing tissues and toothpicks.

In formulating the products of this invention the cold receptor stimulants will be incorporated into a vehicle by means of which the compound may be applied to the person. The vehicle may, itself be completely inert or it may, and usually will, contain other active ingredients. A wide variety of vehicles will be suitable, depending upon the particular product involved, such vehicles include solids, liquids, emulsions, foams and gels. Typical vehicles for the cold receptor stimulants include aqueous or alcoholic solutions, oils and fats such as hydrocarbon oils, fatty acid esters, long chain alcohols and silicone oils; finely divided solids such as starch or talc; cellulosic materials such as paper tissue; low-boiling hydrocarbons and halohydrocarbons used as aerosol propellents; gums and natural or synthetic resins.

Generally, these vehicles will contain at least one or more of the following adjuvants: flavourants, colourants, perfuming agents, surface active agents, antiseptic agents, such as are usually employed in topical and ingestible compositions.

A more detailed discussion of particular products according to this invention follows.

Toiletries and Cosmetics

A major area of utility of the cold receptor stimulants of this invention will be in the field of toilet preparations broadly classed as personal care products. These may be defined as manufactured products applied to the person for the purposes of grooming or hygiene or for cosmetic purposes, including make-up and perfumery, but excluding ethical and proprietary medical preparations. Particular personal care products are discussed hereinafter by way of example and are illustrated in the specific Examples.

One class of personal care product into which the compounds of this invention may be incorporated is represented by lotions for topical application, e.g. after-shave lotions and toilet water where the compound will be used in alcoholic or aqueous alcoholic solution, such solutions usually also containing a perfume or mild antiseptic or both. The amount of compound added to the formulation will usually be in the range 0.1 to 2.5% by weight based on the total composition.

Another class of personal care product is represented by soap and soap-based compositions where the compounds will be used in combination with an oil or fat or a natural or synthetic surfactant e.g. a fatty acid salt or a laurylsulphate salt, the composition usually also containing an essential oil or perfume. The range of soap compositions will include soaps of all kinds e.g. toilet soaps, shaving soaps and shaving foams particularly shaving foams of the aerosol type. Usually the compound will be added to the formulation in amount of from 0.5 to 2.5% by weight.

A further class of personal care products into which the cold receptor stimulants may be incorporated is represented by cosmetic creams, emollients and lotions, such creams, emollients and lotions usually comprising an oil-in-water emulsion as a base and optionally containing a range of other ingredients such as wax, preservative, perfume, atiseptics, astringents and pigments.

Also included within this class are lipstick compositions, such compositions usually comprising an oil and wax base into which the coolant can be incorporated along with other ingredients e.g. pigments. Once again the formulation of such products, apart from the incorporation of the cold receptor stimulant, usually in an amount by weight of from 0.1 to 2.5%.

Personal care products for oral hygiene into which the cold receptor stimulants of this invention can be incorporated include mouthwash, gargle and dentifrice compositions. The first two may be considered together and will usually comprise an aqueous, alcoholic or aqueous-alcoholic solution of an antiseptic often coloured or flavoured for palatability, to which the cold receptor stimulant is added in an amount of from 0.01 to 1.0% by weight.

Dentifrice compositions may be of the solid block, powder, paste or liquid type and will usually comprise a finely divided abrasive or polishing material, e.g. precipitated chalk, silica, magnesium silicate, aluminium hydroxide or other similar materials well known in the art, and a detergent or foaming agent. Optional ingredients which may also be included are flavouring agents and colourants, antiseptics, lubricants, thickeners, emulsifiers or plasticizers. The amount of cold

receptor stimulant added in such compositions will generally be from 0.1 to 2.0% by weight based on the total composition.

Edible and Potable Compositions

The cold receptor stimulants of this invention may be incorporated into a wide range of edible and potable compositions comprising an edible or potable base and usually one or more flavouring or colouring agents. The particular effect of the cold receptor stimulant is to create a cool or fresh sensation in the mouth, and in some cases, even in the stomach, and therefore the compounds find particular utility in sugar-based confectionery such as chocolate, boiled sweets, mints and candy, in ice cream and jellies and in chewing gum. The formulation of such confections will be by traditional techniques and according to conventional recipes and as forms no part of this invention. The cold receptor stimulant will be added to the recipe at a convenient point and in amount sufficient to produce the desired cooling effect in the final product. As already indicated, the amount will vary depending upon the particular compound, the degree of cooling effect desired and the strength of other flavourants in the recipe. For general guidance, however, amounts in the range 0.01 to 1.0% by weight based on the total composition will be found suitable.

Similar considerations apply to the formulation of beverages. Generally speaking the compounds will find most utility in soft drinks, e.g. fruit squashes, lemonade and cola, but may also be used in alcoholic beverages. The amount of compound used will generally be in the range 0.01 to 1.0% by weight based on the total composition.

Medicaments

Because of their cooling effect on the skin and on the mucous membranes of the mouth, throat and nose and of the gastrointestinal tract the cold receptor stimulants may be used in a variety of oral medicines, nasal and throat sprays, and topical compositions, particularly where a counter-irritant is required. Generally speaking, these medical preparations, whether topical or ingestible, proprietary or ethical, will contain a pharmaceutically acceptable carrier, either liquid or solid, a pharmaceutically active ingredient and into these preparations the cold receptor stimulants of this invention can readily be incorporated to provide a pleasant cooling effect on the skin, or other surface tissues of the body, or in the mouth or gastrointestinal tract depending on particular preparation and whether it is to be applied externally or internally. A particular utility for the compounds of this invention is in the formulation of antacid and indigestion remedies, and especially those based on sodium bicarbonate, magnesium oxide,calcium or magnesium carbonate, aluminium or magnesium hydroxide or magnesium trisilicate. In such compositions the compound will usually be added in an amount of from 0.1 to 2.0%.

The cold receptor stimulants may also be included in oral analgesic compositions, e.g. with acetyl salicyclic acid or its salts, and in nasal decongestants e.g. those containing ephedrine.

Tobacco and Tobacco-Containing Preparations

The compounds of this invention also find utility as cold receptor stimulants in tobacco and tobacco-containing manufacturers.

By tobacco and tobacco-containing manufactures we mean any article, such as cigarette or cigar, or any composition, such as pipe or chewing tobacco or snuff, containing tobacco in a prepared form ready for utilisation by the human person whether by smoking, i.e. burning of the prepared tobacco and inhalation of the tobacco smoke, chewing or direct inhalation of the tobacco.

In formulating the tobacco and tobacco-containing manufacturers of this invention the active compound may be incorporated directly into the tobacco, for example, by impregnation of the tobacco with an alcoholic solution of the active ingredient, at a suitable stage of manufacture. However, in an alternative and preferred arrangement, the active ingredient may be incorporated into a tobacco smoke filter for use in a pipe or cigarette filter or as a filter tip for cigarettes. The latter, in particular, forms a particularly effective utilisation of the present invention, the active compound simply being impregnated in the wad of material forming the filter tip. This may be of any of the well known types of filter tip for cigarettes, e.g. a filter pad of cellulose acetate, paper, cotton α-cellulose or asbestos fiber. Conveniently the filter tip is impregnated with an alcoholic solution

of the active compound and then dried to deposit the active compound therein.

The amount of active compound to be incorporated into the tobacco or tobacco-containing manufacture in accordance with the invention will vary from compound to compound depending on the activity thereof, i.e. the amount thereof which it is necessary to place in contact with the skin to produce a noticeable cooling effect, and will depend also on the mode of application thereof, i.e. whether the compound is impregnated in the tobacco itself, or in a filter tip or in any other accessory. However, the actual amount is not critical to this invention and will be readily determinable by the person skilled in the art by means of a few simple tests. As a matter of guidance, however, it may be mentioned that with the more active compounds, as little as 0.1 mg, deposited on the filter tip of a tipped cigarette is effective.

The preparation of compounds used in the present invention is illustrated in the following Examples 1—13.

EXAMPLE 1.

Preparation of 1,7,7-Trimethylbicyclo[2.2.1]heptane-2-carboxylic acid

A Grignard reagent was prepared from endo-2-chloro-1,7,7-trimethylbicyclo[2.2.1]heptane (bornyl chloride, 23.0 g, 0.13 mole), magnesium (3.1 g, 0.13 mole) and THF (100 ml). The mixture was carbonated by bubbling through CO_2 gas overnight. The mixture was then acidified, and extracted with ether. The ether extracts were separated and washed with excess 2N NaOH. The aqueous extracts were acidified and the precipitated acid extracted into ether and dried ($MgSO_4$). Removal of the solvent yielded a white solid (21 g).

EXAMPLE 2.

Preparation of N-Ethyl-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxamide

The product of Example 1 was treated with excess thionyl chloride and then distilled to yield 1,7,7-trimethylbicyclo[2.2.1]heptane-2-carbonyl chloride as a colourless liquid, b.p. 55—60°/0.2 mm. An ether solution of 3.8 g (0.02 mole) of the acid chloride was treated with excess ethylamine (as a 70% solution in water). When reaction was complete, the ether layer was washed with dilute HCl, then with $NaHCO_3$ solution and dried ($MgSO_4$). Removal of the solvent left an oil (4.3 g) which was distilled to yield N-ethyl-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxamide, b.p. 120—4°/0.5 mm as a colourless liquid which rapidly solidifies.

Analysis:	C, 74.1; H, 11.0; N, 6.7 .
Calc.:	C, 74.6; H, 11.0; N, 6.7%.

EXAMPLE 3.

Preparation of N-(1',1'-Dimethyl-2'-hydroxyethyl)-1,7,7-trimethylbicyclo[2.2.1] heptane-2-carboxamide

This was prepared, as in Example 2, from the acid chloride (3.8 g) and excess t-butanolamine in ether solution. The crude product was a white solid which was recrystallised from petroleum ether/chloroform to yield white crystals, m.p. 104—5°.

EXAMPLE 4.

Preparation of 2-Isopropylbicyclo[2.2.1]heptane-2-carboxylic acid

Sodium (5.1 g, 0.22 mole) was dissolved in liquid NH_3 (300 ml) in the presence of a catalytic amount of ferric nitrate. A mixture of isopropyl bromide (26.1 g, 0.22 mole) and bicyclo[2.2.1]heptyl-2-cyanide (25 g, 0.20 mole) was added slowly, and the ammonia left to evaporate overnight. Benzene and water were added, and the organic layer separated and dried ($MgSO_4$). Removal of the solvent left an oil which was distilled to yield 2-isopropylbicyclo[2.2.1]heptyl-2-cyanide (25 g), b.p. 108—110°/10 mm. This was stirred at 120° with 50 mls. of 75% H_2SO_4 and then $NaNO_2$ (23.1 g, 0.35 mole) was added. When the reaction had subsided, water, ether and excess 2N NaOH were added. The ether layer was separated, the aqueous layer was acidified and the precipitated acid extracted into ether and dried ($MgSO_4$). Removal of the solvent and distillation of the crude product yielded 2-isopropylbicyclo[2.2.1]heptane-2-carboxylic acid as a low melting solid, b.p. 112°/0.2 mm.

EXAMPLE 5.

Preparation of N-(2-isopropylbicyclo[2.2.1]heptane-2-carbonyl)glycine ethyl ester.

The product of example 4 was converted, by the method of Example 2 to the acid chloride, b.p. 70—73°/0.1 mm.

To a solution of $NaHCO_3$ (0.64 g, 7.5 mmoles) in water (50 mls) were added ether (50 mls), glycine ethyl ester hydrochloride (0.53 g, 3.75 mmoles) and the acid chloride (0.75 g, 3.75 mmoles). When reaction had ceased the ether layer was separated and dried ($MgSO_4$). Removal of the solvent left a white solid which was recrystallised from 40—60° petroleum to yield N-(2-isopropylbicyclo [2.2.1]heptane-2-carbonyl)glycine ethyl ester, m.p. 112—3°.

Analysis: C, 68.0; H, 9.5; N, 5.3.
Calc.: C, 67.4; H, 9.4; N, 5.2%.

EXAMPLE 6

N-(2-isopropylbicyclo[2.2.1.]heptane-2-carbonyl)morpholine

The acid chloride (1.25 g) was reacted with excess morpholine in ether. When reaction had ceased the ether solution was washed with dilute acid, $NaHCO_3$ solution and then dried ($MgSO_4$). Removal of the solvent left a white solid which was recrystallised from 40—60° petroleum to yield N-(2-isopropylbicyclo[2.2.1]heptane-2-carbonyl)morpholine as white crystals, m.p. 77—79°.

Analysis: C, 71.7; H, 9.9; N, 5.6.
Calc.: C, 71.7; H, 10.0; N, 5.6%.

EXAMPLE 7.

Preparation of 3-Isopropylbicyclo[2.2.1]hept-5-ene-2-carbonyl chloride

4-Methylpent-2-enoic acid was prepared by a Knoevenagl condensation between isobutyraldehyde and malonic acid in pyridine (see 'Organic Functional Group Preparations', Vol. I, by Sandler and Karo, p. 291—220). This was then converted to 4-methylpent-2-enoyl chloride, b.p. 65°/15 mm, with thionyl chloride.

A mixture of freshly distilled cyclopentadiene (27 ml), 4-methylpent-2-enoyl chloride (24 g, 0.18 mole) and toluene (120 ml) was refluxed for 17 hours. The toluene was removed on a rotary evaporator and the residual oil distilled to yield 3-isopropylbicyclo[2.2.1]hept-5-ene-2-carbonyl chloride (26 g, 73%), b.p. 56—60°/ 0.5 mm.

EXAMPLE 8.

Preparation of N,3-Diisopropylbicyclo[2.2.1]hept-5-ene-2-carboxamide

The product of Example 7 (2 g) was reacted with excess isopropylamine in ether (100 m l). When reaction had ceased, the solution was washed with dilute acid $NaHCO_3$ solution and dried ($MgSO_4$). Removal of the solvent yielded a white solid, which was recrystallised from 40—60° petroleum/CH_2Cl_2 to yield N,3-diisopropylbicyclo[2.2.1]hept-5-ene-2-carboxamide as white crystals, m.p. 110—111°.

EXAMPLE 9.

Preparation of 3-isopropylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid 2'-hydroxyethyl ester.

A mixture of ethylene glycol (6 g), triethylamine (2 g) and the product of Example 7 (2 g) in acetone (100 ml) was stirred at room temperature overnight. Ether and dilute acid were added. The ether layer was separated, washed with $NaHCO_3$ solution and dried ($MgSO_4$). Removal of the solvent left an oil which was distilled to yield the 2'-hydroxyethyl ester of 3-isopropylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid, b.p. 94—8°/0.02 mm as a colourless liquid.

EXAMPLE 10.

Preparationof 2-Methylbicyclo[2.2.2]oct-5-ene-2-carbonyl chloride

A mixture of ethyl methacrylate (14.3 g, 0.13 mole), 1,3-cyclohexadiene (10 g, 0.13 mole) and p-hydroquinone (1 g) was heated, in a 75 ml, steel autoclave, to 170° for 26 hours. Distillation of the crude product yielded ethyl-2-methylbicyclo[2.2.2]oct-5-ene-2-carboxylate (11 g, 45%) as a colourless liquid, bp. 60—70°/0.2 mm. This was deesterfied by heating with NaOH in diethylene glycol (140°, 17 hours) to yield 2-methylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid (9.5 g) as a solid which was purified by sublimation at 100°/0.02 mm. Treatment with

thionyl chloride yielded 2-methylbicyclo[2.2.2]oct-5-ene-2-carbonyl chloride, b.p. 56—62°/0.2 mm, as a colourless liquid.

EXAMPLE 11.

Preparation of N-Ethyl-2-methylbicyclo[2.2.2]oct-5-ene-2-carboxamide

Treatment of the acid chloride, prepared in Example 10, with excess ethylamine as in Example 2, yielded N-ethyl-2-methylbicyclo[2.2.2]oct-5-ene-2-carboxamide as white crystals, m.p. 90—91° (recrystallised from 40—60° petroleum).

Analysis: C, 74.6; H. 10.1; N.7.2.
Calc.: C, 74.6; H, 9.8; N, 7.3%.

EXAMPLE 12.

Preparation of 6,6-Dimethylbicyclo[3.1.1]heptane-2-carboxylic acid

Aluminium trichloride (22.4 g) was suspended in diglyme (500 ml) and sodium borohydride (19 g) was added slowly, followed by dropwise addition of α-pinene (81.6 g). After 4 hours the mixture was hydrolysed with 2NHCl, extracted with ether and dried ($MgSO_4$). Removal of the solvent left an oil, which was treated with a solution of NaOH (16 g) in ethanol (400 ml), and hydrogen peroxide (136 g, of 30% solution) was added at such a rate as to maintain a steady reflux. When reaction had ceased, most of the ethanol was removed by evaporation, the residue was extracted with ether and dried ($MgSO_4$). Removal of the solvent yielded crude 6,6-di-methylbicyclo[3.1.1]heptyl-2-methanol.

The crude methanol was dissolved in ether (500 ml) and chromic acid (prepared from 200 g $Na_2Cr_2O_7$ in 600 ml water, to which was added 272 g H_2SO_4 and the whole made up to 1 litre) added dropwise, with stirring, at such a rate as to maintain the temperature of the mixture at 20—25°C. When the solution turned red, addition of the chromic acid was stopped. The ether layer was separated, the aqueous layer extracted with more ether, the combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Removal of the solvent left an oil which was distilled to yield 6,6-dimethyl-bicyclo[3.1.1]heptane-2-carboxylic acid (20 g), b.p. 79°/0.005 mm.

EXAMPLE 13.

N-t-Butyl-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxamide

Treatment of the product of Example 12 with thionyl chloride yielded 6,6-dimethylbicyclo[3.1.1]heptane-2-carbonyl chloride, b.p. 61°/0.2 mm. This acid chloride (1.0 g) was reacted with excess t-butylamine in ether as in Example 8, to yield N-t-butyl-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxamide as a viscous liquid, b.p. 89—90°/0.005 mm.

Typical consumer products, containing a cooling compound, according to this invention are illustrated in Examples 14—32.

EXAMPLE 14.

After-Shave Lotion

An after-shave lotion was prepared according to the following recipe by dissolution of the ingredients in the liquid and cooling and filtering:

Denatured ethanol	75%
Diethylphthalate	1.0%
Propylene Glycol	1.0%
Lactic Acid	1.0%
Perfume	3.0%
Water	to 100%

Into a sample of the base lotion was added 1.0% by weight based on the weight of the same of N-ethyl-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxamide.

When the final solution was applied to the face a clearly noticeable cooling effect became apparent after a short interval of time.

EXAMPLE 15.

Cleansing Tissue

A cleansing liquid was prepared having the formulation:

Triethanolamine lauryl sulphate	1.0%
Glycerol	2.0%
Perfume	.95%
Water	to 100%

To this liquid was added 2% of 1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxylic acid. A paper tissue was then soaked in the liquid.

When the impregnated tissue was used to wipe the skin a fresh cool sensation developed on the skin after a short interval.

EXAMPLE 16.

Toothpaste

The following ingredients were mixed in a blender:

Dicalcium phosphate	48.0%
Sodium lauryl sulphate	2.5%
Glycerol	24.8%
Sodium carboxymethyl cellulose	2.0%
Citrus flavourant	1.0%
Sodium saccharin	0.5%
Water	to 100%

Shortly before completion of the blending operation 1% by weight of N-ethyl-2-isopentylbicyclo[2.2.1]heptane-2-carboxamide was added to the blender.

When applied as a toothpaste a pleasant cooling effect is noticed in the mouth.

EXAMPLE 17.

Aerosol Shaving Soap

An aerosol shaving soap composition was formulated according to the following recipe:

Stearic acid	6.3%
Lauric acid	2.7%
Triethanolamine	4.6%
Sodium carboxymethyl cellulose	0.1%
Sorbitol	5.0%
Water	to 100%
Perfume	0.5%

The composition was prepared by fusing the acids in water, adding the triethanolamine, cooling and adding the other constituents. To the mixture was then added 0.5% of N-ethyl-1,3,3-trimethylbicyclo[2.2.1]heptane-2-carboxamide. The composition was then packaged in an aerosol dispenser under pressure of a butane propellent.

EXAMPLE 18.

Hair Shampoo

Sodium lauryl ether sulphate, 10 g., was dispersed in 90 g. water in a high speed mill. To the dispersion was added 2.0% by weight of 2-isopentyl-bicyclo[2.2.1]hept-2-yl methanol. When the hair is washed using the shampoo a fresh, cool sensation is noticed on the scalp.

EXAMPLE 19.

Toothpick

The tip of a wooden toothpick was impregnated with an alcoholic solution containing 3,3-dimethylbicyclo[2.2.1]heptane-2-carboxylic acid 2'-hydroxyethyl ester in an amount sufficient to deposition on the toothpick 0.1 mg of the compound. The toothpick was then dried.

When placed against the tongue a cool sensation is noticed after a short period of time.

EXAMPLE 20.

Soft Drink

A soft drink concentrate was prepared from the following recipe:

Pure orange juice	60%
Sucrose	10%
Saccharin	0.2%
Orange flavouring	0.1%
Citric acid	0.2%
sulphur dioxide	Trace amount
Water	to 100%

To the concentrate was added 0.1% of N-ethyl-2,3-dimethyl-bicyclo[2.2.1]hept-5-ene-2-carboxamide.

The concentrate was diluted with water and tasted. An orange flavour having a pleasantly cool after-effect was obtained.

EXAMPLE 21.

Toilet Water

A toilet water was prepared according to the following recipe:

Denatured ethanol	75.0%
Perfume	5.0%
Water	to 100%

To the recipe was added 3.0% based on the total composition, of N,N-dimethyl-3-methylbicyclo[2.2.1]hept-5-ene-2-carboxamide.

As with the after shave lotion, a cooling effect was clearly noticeable on the skin well after the termination of any cooling effect attributable to the evaporation of the alcoholic carrier.

EXAMPLE 22.

Soft Sweet

Water was added to icing sugar at 40°C to form a stiff paste. 2-*n*-Propylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid 2'-hydroxyethyl ester (0.2%) was then stirred into the paste and the mixture allowed to set. A soft sweet mass resulted having the characteristic cooling effect in the mouth of peppermint but without the minty flavour or odour.

EXAMPLE 23.

Hydrophilic Ointment

A hydropholic ointment was prepared having the following formulation:

Propylene Glycol	12%
1-Octadecanol	25%
White soft paraffin	25%
Sodium lauryl sulphate	1%
Water	to 100%

The sodium lauryl sulphate was added to the water and heated to 60°C. The paraffin was melted by heating to 60°C and was then added to the sodium lauryl sulphate mixture with stirring. Propylene glycol and 1-octadecanol was then added to this mixture.

To the resultant mixture was added 2.0% of N-(3-isopropylbicycl[2.2.1]hept-5-ene-2-carbonyl)glycine ethyl ester.

The final ointment when applied to the skin gave rise to a marked cooling effect.

EXAMPLE 24.

Deodorant Composition

A deodorant composition suitable for formulation and dispensing as an aerosol under pressure of a suitable propellent was formulated according to the following recipe:

Denatured ethanol	96.9%
Hexachlorophene	2.0%
Isopropyl myristate	1.0%
Perfume	0.1%

To the composition was added 2.0% by weight of N-ethyl-2-methyl-bicyclo[2.2.2]oct-5-ene-2-carboxamide.

Application of the final composition gave rise to a definite cooling sensation on the skin.

EXAMPLE 25.

Lipstick

0.1% by weight of N-1',1'-dimethyl-2'-hydroxyethyl)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2-carboxamide was incorporated into a proprietary lipstick by melting the lipstick, adding the compound, and allowing the lipstick to resolidify. When applied to the lips a persistent cooling effect is clearly noticeable.

EXAMPLE 26.

Solid Cologne

A solid cologne was formulated according to the following recipe:

Denatured ethanol	74.5%
Propylene glycol	3.0%
Sodium stearate	5.0%
Perfume	5.0%
Water	to 100%

The sodium stearate was dissolved by stirring in a warm mixture of the ethanol, propylene glycol and water. To the solution was added the perfume and

2.0% of N-(2-isopropylbicyclo[2.2.1]heptane-2-carbonyl)morpholine, and the mixture then allowed to solidify into a waxy cake.

When applied to the forehead a strong cooling effect is obtained.

EXAMPLE 27.

Hair Tonic

A hair tonic was formulated containing:

Denatured ethanol	84.5%
Castor oil	14.0%
Resorcinol	0.5%
Perfume	1.0%

The castor oil, resorcinol and perfumes were dissolved in the ethanol component and to the solution was added 2.0% of N-methyl-2-isopentylbicyclo[2.2.1]heptane-2-carboxamide. When rubbed on the scalp a cooling effect is noticed.

EXAMPLE 28.

Mouthwash

A concentrated mouthwash composition was prepared according to the following recipe:

Ethanol	3.0%
Borax	2.0%
Sodium bicarbonate	1.0%
Glycerol	10.0%
Flavourant	0.4%
Thymol	0.03%
Water	to 100%

To the composition was added 0.1% of N-ethyl-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxamide. When diluted with approximately 10 times its own volume of water and used to rinse the mouth a strong cooling effect is obtained in the mouth.

EXAMPLE 29.

Talcum Powder

A talcum powder was prepared by grinding together the following:

Low micron talc	90%
Zinc stearate	5%
Starch	5%

In the course of grinding there was added 5.0% of N-isopropyl-3-methylbicyclo[2.2.2]oct-5-ene-2-carboxamide. A talcum powder having a freshening and cooling effect was obtained.

EXAMPLE 30.

Chewing Gum

Leaves of a proprietary chewing gum were leached in running water for 168 hours to remove all water-soluble flavourants. At the end of the leaching operation the chewing gum base had no detectable minty odour or flavour. The chewing gum base was then kneaded with 0.2% of 2-isopropylbicyclo[2.2.1]heptane-2-

carboxylic acid. When compared with the water-extracted chewing gum base, the final product showed not distinguishable change in flavour but showed a marked cooling effect in the mouth.

EXAMPLE 31.

A proprietary brand of cigarette tobacco was sprayed with an ethanolic solutionof N-ethyl-1,7,7-trimethylbicyclo[2.2.1]heptane-2-carboxamide and was rolled into cigarettes each containing approximately 1 mg. of active compound. Smoking the impregnated cigarettes produced a cool effect in the mouth characteristic of mentholated cigarettes but without any attendant odour other than the normally associated with tobacco.

EXAMPLE 32.

Filter Tip Cigarette

The filter tip of a proprietary brand of cigarette was impregnated with an ethanolic solution of N-ethyl-3,3-dimethylbicyclo[2.2.1]hept-5-ene-2-carboxamide in an amount sufficient to deposit in the filter 1 mg. of the active compound. Smoking the cigarette with the impregnated tip gave rise to a noticeable cooling effect in the mouth.

The above Examples 14—32 illustrate the wide range of consumer products into which the physiologically active compounds of this invention may be incorporated to impart to those compounds the capability of stimulating the cold receptors of the nervous system to produce a cool sensation when those products are applied to or consumed by the human person. Similar cooling effects may be obtained with any of the bicyclic compounds hereinbefore described.

The compounds used in accordance with the present inventon as cold receptor stimulants may also be used in ingestible compositions, and in tobacco, to modify the flavour thereof in amounts below that at which the cooling activity is noticeable. This alternative usage, as flavour modifiers, is described and claimed in our copending Application No. 22833/76 (Serial No. 1,502,706).

WHAT WE CLAIM IS:—

1. A manufactured consumer product for application to or consumption by the human body, into which there is incorporated, in an amount effective to stimulate the cold receptors of the nervous system of the body when brought into contact therewith upon use of the product, a compound of the formula RX, where

R is a saturated or monoethylenically unsaturated alkyl-substituted bicyclic hydrocarbon radical containing a total of from 8—12 carbon atoms and selected from [3.1.1]bicycloheptanes, [2.2.1]bicycloheptanes and hept-5-enes and [2.2.2]bicyclooctanes and oct-5-enes containing from 1—3 C_1—C_5 alkyl substituents;

X is a CH_2OH, COOH, $COOR_1$ or $CONR_2R_3$ group attached to said bicyclic radical at a 2-position, and where

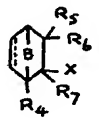
R_1 is a hydroxyalkyl or hydroxyalkoxyalkyl radical of from 2—4 carbon atoms;

R_2, when taken separately, is H or C_1—C_5 alkyl;

R_3, when taken separately, is H, C_1—C_5 alkyl, C_1—C_5 hydroxyalkyl or C_3—C_6 alkoxycarbonylalkyl, with the proviso that when R_1 is H, then R_2 may also be C_3—C_6 cycloalkyl, phenyl or phenyl containing up to 2 hydroxy, methyl or methoxy substituents; and

R_2 and R_3, when taken together, represent a C_4—C_5 alkylene group, the carbon atom chain of which may optionally contain an ether oxygen atom, and forming with the nitrogen to which they are attached a piperidino-, pyrollidino or morpholino group.

2. A product according to claim 1, wherein said compound is of the formula



where B is a bridging group selected from —CH_2— and —$C(CH_3)_2$—;

the broken line represents an optional ethylenically unsaturated valency bond;

R_4 is H or Ch_3;

R_5 is H or CH_3;
R_6 is H or C_1—C_3 alkyl;
R_7 is H or C_1—C_5 alkyl;
X is as defined in claim 1;
it being provided i) that when B is —CH_2— then at least one, but no more than 3 of R_4—R_7, is alkyl, R_4—R_7 together providing a total of from 1—5 carbon atoms; and ii) that when B is —$C(CH_3)_2$—, then R_4 is —CH_3 and R_5—R_7 are all H.

3. A personal care product as hereinbefore defined containing a means for stimulating the cold receptors of the nervous system of the human body, wherein said means comprise an effective amount of compound of the formula defined in claim 1.

4. A dentifrice containing a means for stimulating the cold receptors of the nervous system of the surface tissues of the mouth, wherein said means comprise an effective amount of a compound of the formula defined in claim 1.

5. A toilet lotion comprising a liquid vehicle selected from the following: water, alcohol and mixtures thereof, and an adjuvant selected from the following: an antiseptic, perfuming agent and colourant and mixtures thereof, and containing means for stimulating the cold receptors of the nervous system of the skin wherein said means comprise an effective amount of a compound of the formula defined in claim 1.

6. A cosmetic preparation comprising an oil-in-water emulsion and an adjuvant selected from the following: an antiseptic, perfuming agent and colourant and mixtures thereof, and containing means for stimulating the cold receptors of the nervous system of the skin wherein said means comprise an effective amount of a compound of the formula defined in claim 1.

7. A toilet preparation comprising a foamable base containing a surfactant selected from the following: soap, synthetic surfactants and mixtures thereof and containing means for stimulating the cold receptors of the nervous system of the skin wherein said means comprise an effective amount of a compound of the formula defined in claim 1.

8. A cleansing tissue comprising a tissue impregnated with a cleansing liquid and containing a means for stimulating the cold receptors of the nervous system of the skin, wherein said means comprises an effective amount of a compound of the formula defined in claim 1.

9. A toothpick coated or impregnated with a means for stimulating the cold receptors of the nervous system of the mouth, wherein said means comprises an effective amount of a compound of the formula defined in claim 1.

10. An edible preparation comprising an edible base, and an adjuvant selected from flavourants and colourants and mixtures thereof, and containing a means for stimulating the cold receptors of the nervous system of the surface tissues of the mouth, wherein said means comprises an effective amount of a compound of the formula defined in claim 1.

11. A chewing gum containing a means for stimulating the cold receptors of the nervous system of the surface tissues of the mouth, wherein said means comprise an effective amount of a compound of the formula defined in claim 1.

12. A potable preparation comprising a potable base, and an adjuvant selected from flavourants and colourants and mixtures thereof, and containing a means for stimulating the cold receptors of the nervous system of the surface tissues of the mouth, wherein said means comprise an effective amount of a compound of the formula defined in claim 1.

13. A pharmaceutical preparation comprising pharmaceutically acceptable carrier, a pharmaceutically active ingredient and a means for stimulating the cold receptors of the nervous system of the human body wherein said means comprise an effective amount of a compound of the formula defined in claim 1.

14. A tobacco or tobacco-containing manufacture comprising tobacco and an agent capable of stimulating the cold receptors of the nervous system of the nasal or oral mucosa when brought into contact therewith upon use of the manufacture, wherein said agent comprises an effective amount of a cold receptor stimulating bicyclic alcohol, acid, ester or amide of the formula defined in claim 1.

15. Tobacco impregnated with an amount of a cold receptor stimulant effective to stimulate the cold receptors of the nervous system of the oral or nasal mucosa when said tobacco, or the smoke therefrom, is in contact therewith, wherein said stimulant is a cold receptor stimulating bicyclic alcohol, acid, ester or amide as defined in claim 1.

16. A cigarette containing an amount of a cold receptor stimulant effective to

stimulate the cold receptors of the nervous system of the oral or nasal mucosa when the cigarette is smoked, wherein said stimulant is a cold receptor stimulating bicyclic alcohol, acid, ester or amide as defined in claim 1.

17. A filter-tipped cigarette comprising a filter tip, a tobacco-containing body, and an amount of a cold receptor stimulant effective to stimulate the cold receptors of the nervous system of the oral or nasal mucosa when the cigarette is smoked, wherein said stimulant is a cold receptor stimulating bicyclic alcohol, acid, ester or amide as defined in claim 1, which is impregnated in said filter tip.

18. A method of imparting to a consumer product for application to or consumption by the human body the property of stimulating the cold receptors of the nervous system of the human body, which comprises incorporating into a consumer product base an effective amount of a compound of the formula defined in claim 1.

19. A method of stimulating the cold receptors of the nervous system of the human body other than for medical purposes which comprises applying thereto an effective amount of a compound of the formula defined in claim 1.

20. An article, method or preparation, as the case may be, according to any one of claims 3—19, wherein the cold receptor stimulant is as defined in claim 2.

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